REMARKS

Claims 21, 31 and 32 have been amended, and claims 33-48 have been withdrawn. Claim 23 has been canceled by Applicants. Claims 21, 22, 24 and 29-32 are thus pending in this application.

Claim 21 has been amended remove the limitation "and wherein said antibody synergistically enhances APC-mediated human CTL activation." Claim 21 has further been amended to recite specific hybridomas that have been deposited with the American Type Culture Collection (ATCC), and which produce anti-CD40 antibodies capable of blocking binding of CD40L on a human T lymphocyte to CD40 on a human APC by 16-88% and enhancing APC-mediated human CTL activation, in accordance with claim 21. The hybridomas were generated and tested by the methods of the invention as described in Examples 1-6 of the specification. The hybridomas correspond to the clones as cited in the specification at page 5, line 10, and in Figures 1A-5B. The following table sets forth the clone number, hybridoma reference number, and ATCC deposit accession numbers, as well as the areas in the specification that provide support for each clone:

CLONE	HYBRIDOMA REFERENCE NO.	ATCC DEPOSIT ACCESSION NO.	SUPPORT IN SPECIFICATION
clone 4	hybridoma MAb 186-4-1	PTA-2996	Figures 1a-b, 3, 4, 5a-b
clone 7	hybridoma MAb 186-7-2	PTA-2997	p. 5, line 10; Figures 1a-b, 2a-d, 3, 4, 5a-b
clone 15	hybridoma MAb 186-15-1	PTA-2998	p. 5, line 10; Figures 1a-b, 2a-d, 3, 4, 5a-b
clone 21	hybridoma MAb 186-21-1	PTA-2993	p. 5, line 10; Figures 1a-b, 2a-d, 3, 4, 5a-b
clone 26	hybridoma MAb 186-26-3	PTA-2999	Figures 1a-b
clone	hybridoma MAb 186-64-1	PTA-2994	p. 5, line 10; Figures 1a-b, 2a-

64			d, 3, 4, 5a-b
clone 70	hybridoma MAb 186-70-3	PTA-2995	p. 5, line 10; Figures 1a-b, 2a-d, 3, 4, 5a-b

Claim 24 has been amended to remove the limitation "or an antibody in which the potential T cell epitopes have been eliminated."

Claim 31 has been amended to recite specific hybridomas that have been deposited with the American Type Culture Collection (ATCC), and which produce antibodies capable of binding the CD40 receptor and blocking binding of CD40L on a human T lymphocyte to CD40 on a human APC by 16-88%, in accordance with claim 31. The hybridomas were generated and tested by the methods of the invention as described in Examples 1-6 of the specification. The hybridomas correspond to the clones as cited in the specification at page 5, line 10, and in Figures 1A-5B, as follows, in relation to the hybridoma depositor reference and ATCC deposit accession numbers: clone 4 (hybridoma MAb 186-4-1, ATCC Accession No. PTA-2996), clone 7 (hybridoma MAb 186-7-2, ATCC Accession No. PTA-2997), clone 15 (hybridoma MAb 186-15-1, ATCC Accession No. PTA-2998), clone 21 (hybridoma MAb 186-21-1, ATCC Accession No. PTA-2993), clone 26 (hybridoma MAb 186-26-3, ATCC Accession No. PTA-2999), clone 64 (hybridoma MAb 186-64-1, ATCC Accession No. PTA-2994), clone 70 (hybridoma MAb 186-70-3, ATCC Accession No. PTA-2995).

Claims 31 and 32 have been amended to substitute the word "lymphocyte" for the word "cell" in the phrase "cytotoxic T cell."

As per the Examiner's request, the specification has been amended to add a statement relating to the deposited biological material to the effect that "all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a U.S. patent based upon this application."

The specification has been amended to delete reference to Table 1 in the section at page 18, line 22 - page 19, line 12 ("Example 2"), because, as far as we have been able to determine, the originally-filed specification actually did not include Table 1. The data contained in the missing Table 1 merely served to illustrate that the procedure set forth in Example 1 ("Generation of mouse anti-human CD40 monoclonal antibodies") yielded 69 wells (out of 4896 total wells) with supernatants containing anti-human CD40-specific antibodies. This data is not required to adequately describe or enable the claimed invention, particularly in view of the hybridoma deposits now recited in the claims. Therefore, deletion of the reference to Table 1 does not affect the patentability of the pending claims.

No new matter has been introduced in these amendments. Upon entry of these amendments, claims 21-24 and 29-32 will be pending. Entry and consideration of these amendments is respectfully requested.

Rejection under 35 U.S.C. § 112, first paragraph, lack of written description

The Examiner has rejected claims 21-24 and 29-32 under 35 U.S.C. § 112, first paragraph, for allegedly lacking adequate written description in the specification as filed. The examiner believes that the specification does not provide support for amendments made in the last Response: (1) "wherein said anti-CD40 antibody or binding fragment is capable of blocking binding of CD40L on a human T lymphocyte to CD40 on a human APC by 16-88% and wherein said antibody synergistically enhances APC-mediated human CTL activation" in claim 21; (2) "with an antibody or binding fragment thereof that binds to said receptor and blocks binding of CD40L to CD40 by 16-88%" in claim 31; (3) "wherein said antibody or binding fragment thereof blocks binding of CD40L to CD40 by 16-25%" in claim 32; and (4) "an antibody in which the potential T cell epitopes have been eliminated" in claim 24. The Examiner has expressed concern that the claims are directed to an overly broad subgenus.

Applicants respectfully disagree. First, in order to advance prosecution, claim 21 has been amended remove the limitation "and wherein said antibody synergistically enhances APC-

mediated human CTL activation." Therefore, the rejection as it relates to that limitation of claim 21 has been mooted by this amendment.

Second, three of the four limitations in question are adequately described in the specification as filed: (1) the specification, in Example 4, which appears at page 22, clearly describes blocking of CD40L by up to 88% with the antibody produced by clone 4 (ATCC Accession No. PTA-2996), and blocking of CD40L by 16% with the antibody produced by clone 7 (ATCC Accession No. PTA-2997) -- thus, the specification describes anti-CD40 antibody or binding fragment-facilitated blocking of binding of CD40L on a human T lymphocyte to CD40 on a human APC by 16-88%; and (2) the specification, also at Example 4, page 22, clearly describes blocking of CD40L by 25% with the antibody produced by clone 64 (ATCC Accession No. PTA-2994) -- thus, the specification describes the situation where an antibody or binding fragment thereof blocks binding of CD40L to CD40 by 16-25%. See Example 4 at page 22.

To advance prosecution claim 24 has been amended to remove the language "an antibody in which the potential T cell epitopes have been eliminated." Therefore, the rejection of claim 24 has been mooted by this amendment.

In response, the pending claims have been amended to recite specific hybridomas that produce antibodies according to the claimed invention.

Rejection under 35 U.S.C. § 112, first paragraph, lack of enablement

The examiner rejected claims 21-24 and 29-30 under 35 U.S.C. § 112, first paragraph, for alleged lack of enablement, citing reasons of record (Office action at page 5, item 6).

The examiner has reiterated his previous argument that the specification allegedly does not teach how to induce antigen-specific cytotoxic T lymphocyte responses in the absence of co-administering an activating antigen, as taught by Melief (US 2003/0022860).

The examiner alleges that "conditions boosting a weak immune response with the administration of anti-CD40 antibodies in the absence of antigen are not readily apparent in the disclosure" and "do not appear to be consistent with Applicant's own Example 3 and the teachings of Melief et al."

In response, Applicants respectfully suggest that the Examiner has misread the specification by unduly combining Example 3 with Melief to unjustifiably conclude, contrary to the invention, that co-administration of antigen is essential. Melief is not part of the invention, and should not be combined with the disclosure as if it were. Rather, the invention is an advance from Melief. First, the co-administration of antigen is not disclosed as proposed by the Examiner. There is no disclosure in the specification that co-administration of an antigen is essential to the claimed methods. Example 3 represents one embodiment of the claimed method: co-administration of antigen is optional, and may in some cases be preferred. It is not essential to any and all embodiments of the invention.

Secondly, Example 3 represents an assay that is used to model real world conditions and show enablement of the claimed method. To do so, an antigen is provided as a substitute for a foreign antigen that would have already been present in an individual in need of enhancement of a CTL response according to the claimed invention. One of ordinary skill in the art, seeking to enhance the immune response to an antigen in the system of a patient, would understand this fact, and would be able to use the claimed methods as taught in the specification, without the need to administer antigen to the patient, *because the antigen in question would already be present in a patient in need of such therapy.* The artisan would not understand that treatment for a foreign antigen would require administration of antigen.

Third, Melief teaches away from the claimed methods. The methods disclosed in Melief require the co-administration of an antigen in order to achieve an antigen-specific enhanced CTL response, i.e., a response to the antigen that is administered. The presently claimed method is not directed to an antigen-specific response but instead is for enhancing a response to any foreign antigen that is already present in the system of the individual being administered the anti-CD40

antibody. See the Abstract of the Specification at page 27. See also the specification, Example 3 at page 21, lines 9-11. Therefore, the methods of the present invention are enabled to the skilled artisan, because an artisan seeking to enhance an immune response in an individual need not determine the antigen to which an immune response is to be mounted, or co-administer antigen, in order to practice the methods as claimed. Instead, the artisan can simply apply the agonist anti-CD40 antibodies of the invention as taught in the specification.

In addition, Applicants note that antigen uptake by APCs, an event in Melief that is stimulated by the administration of antigen, is a separate event from APC stimulation and interaction of APCs with T cells. As described in the specification's background of the invention, APCs take up antigen at sites of antigen introduction, and process the antigen. This activates the APC, which then circulate to the lymph nodes, where they present antigen to T cells. Activation of APCs and enhancement of the APC-T cell interaction, therefore, do not happen simultaneously with antigen uptake. By this reasoning, there is no clear advantage nor need to co-administer antigen along with the anti-CD40 antibodies of the methods as claimed. The methods of the claims treat the events of APC stimulation and enhancement of CTL response. It is not essential that the methods further provide for presentation of antigen for uptake by APCs; therefore, the specification need not enable this step as it is not necessary to practice the invention and enhance an APC-mediated CTL response. Indeed, the focus of the claimed methods is to enhance the immune response to an antigen that an individual has already acquired as part of a disease state.

Accordingly, Applicants submit that the specification is enabling to those of skill in the art to make and use the claimed method for enhancing an immune response in the absence of administered antigen.

Rejection under 35 U.S.C. § 102(e)

The Examiner has rejected claims 21-24 and 30-32 under 35 U.S.C. § 102(e) as allegedly anticipated by Melief *et al.* (US 2003/0022860) ("Melief"). The Examiner argues that Melief teaches the use of agonistic anti-CD40 antibodies for enhancing immune responses.

Anticipation requires that each and every element of the rejected claim(s) be disclosed in a single prior art reference. See MPEP 2131 (8th Ed. Rev. 2, May 2004). "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). Every element of the claimed invention must literally be present, arranged as in the claim. *Perkin Elmer Corp. v. Computervision Corp.*, 732 F.2d 888, 894, 221 USPQ 669, 673 (Fed. Cir. 1984).

Applicants respond that Melief fails to teach all of the limitations of the present invention.

First, Applicants have amended the pending claims to recite specific hybridomas that are capable of producing antibodies according to the claimed invention. Melief fails to teach any of the claimed hybridomas. In addition, the disclosure in an allegedly anticipating reference must provide and enable one of skill in the art to produce the claimed subject matter without undue experimentation. "Mere naming or description of the subject matter is insufficient." *Elan Pharm., Inc. v. Mayo Found. For Med. Educ. & Research*, 346 F.3d 1051, 1054, 68 USPQ2d 1373, 1376 (Fed. Cir. 2003); MPEP 2121.01. The very general teaching concerning anti-human CD40 antibodies found in Melief at paragraph [0029] constitutes mere naming or description of a human anti-human CD40 genus, and is thus not enabling. Therefore, the Melief disclosure cannot anticipate the specific anti-human CD40-producing hybridomas recited in the claims.

Additionally, Applicants submit that the agonist antibody disclosed in Melief differs substantially, and thus does not anticipate, the antibodies or uses thereof of the claims presented herein.

Applicants submit that the agonist antibody disclosed in Melief is unrelated to the antibodies of the instant invention, in type, in species cross-reactivity, and in function. Melief describes the use of FGK45, a *rat anti-mouse* monoclonal antibody (see www.alexis-corp.com/apoptosis-ALX-805-046/opfa.1.1.ALX-805-046.1.4.1.html, previously submitted in

connection with Applicants' October 12, 2005 Response to a July 12, 2005 Office Action in this case). FGK45 is a rat antibody that recognizes *mouse* CD40. In contrast, the instant application relates to *mouse anti-human* monoclonal antibodies, which are mouse antibodies that recognize *human* CD40, and specific hybridomas that produce them.

The agonist antibody disclosed in Melief is also functionally distinct from the antibodies of the present claims. The antibodies of the claims activate CD40 in addition to blocking CD40-CD40L interaction by 16-88% (see the specification at page 18, line 26 to page 19, line 3, and page 22, lines 19-20). In contrast, FGK45 activates CD40 but does not block CD40 binding to CD40L, Example 2, page 4, paragraph [0041] of Melief, wherein the ability of T_{helper} cells to interact with APCs through the CD40-CD40L pathway was blocked by the CD40L-blocking antibody MR1, and not FGK45. Indeed, not only was FGK45 not used to achieve the CD40-CD40L blockade, but the defect that was induced by the CD40-CD40L blockade was fully restored following CD40 signaling by the FGK45. As FGK45 does not block binding, Applicants submit that the claimed antibodies of the invention cannot be anticipated by any reference to FGK45, nor by any broad and unspecific reference to human or humanized antibodies. Thus, the antibodies and methods of the invention are not anticipated by Melief's disclosure of FGK45.

Melief does not teach every element of the claims as amended, and cannot anticipate the present invention. Therefore, Applicants submit that the claims are not anticipated by Melief, and respectfully request that the rejection under 35 U.S.C. § 102(e) be withdrawn. Accordingly, Applicants submit that Melief does not teach all of the limitations of claims 21-24 and 30-32, and thus cannot anticipate the present invention.

Rejection under 35 U.S.C. § 103(a)

The Examiner has rejected claims 21-24 and 30-32 under 35 U.S.C. § 103(a) as allegedly obvious over Melief in view of Zhou *et al.* (Hybridoma 1999, 18:471-488) ("Zhou") and/or Caux *et al.* (*Research in Immunology* 1994, 145:235-239) ("Caux") and/or Katira *et al.* (Leukocyte Typing V, Schlossman *et al.*, Ed.) ("Katira") and/or Schwabe *et al.* (*Hybridoma* 1997, 16:217-226)

("Schwabe"). The Examiner alleges that Melief teaches methods of treating tumors or infectious diseases comprising administering anti-CD40 antibodies or fragments to generate or enhance immune responses. In particular, the Examiner argues that Melief discloses the anti-CD40 antibody FGK45, and that the remaining references teach that a number of agonistic anti-CD40 antibodies were well-known in the art. The Examiner alleges that it would be obvious to combine the teachings of Melief and, for example, Schwabe, to reach the present invention.

The Examiner has also rejected claim 29 under 35 U.S.C. § 103(a) as allegedly obvious over Melief in view of Zhou and/or Caux and/or Katira and/or Schwabe as applied above, and further in view of Maraskovsky *et al.* (U.S. Patent No. 6,497,876) ("Maraskovsky"). The Examiner alleges that Maraskovsky teaches the missing limitation of the use of interferon-γ to treat tumors and infections. The Examiner argues that it would be obvious to combine the teachings of these references to reach the present invention.

To establish a *prima facie* case of obviousness, the Examiner must meet three criteria. The Examiner must establish that (1) there is some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; (2) there is a reasonable expectation of success; and (3) the prior art reference (or references when combined) teach or suggest all the claim limitations. See MPEP 706.02(j) and 2143. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on Applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 U.S.P.Q2d 1438 (Fed. Cir. 1991).

Here, neither Melief nor any of the other cited references teach all of the limitations of the present invention because they do not teach or suggest the claimed anti-CD40 antibodies of the invention, which agonize CD40 and are able to block the binding of CD40 to CD40L by 16-88%. None of the cited references have these limitations, and it would not be obvious to generate or search for an antibody that activates CD40 and also blocks CD40:CD40L binding within the specified percent range.

Similarly, the remaining references (Zhou, Caux, Katira, Schwabe, and Maraskovsky) fail to provide the missing limitations, and provide no suggestion or motivation to combine with Melief, or any other reference, to generate such antibodies. The Examiner has failed to satisfy all three prongs of the test outlined above, and accordingly, has not established a *prima facie* case of obviousness.

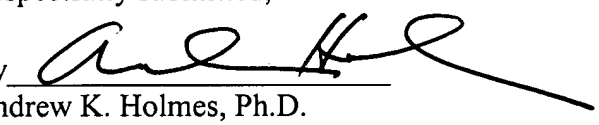
In view of the foregoing, Applicants respectfully submit that all claims as herein presented are non-obvious. Accordingly, Applicants respectfully request that the rejections under 35 U.S.C. § 103(a) be withdrawn.

CONCLUSION

In view of the above amendments and remarks, it is respectfully requested that the application be reconsidered and that all pending claims be allowed and the case passed to issue. If there are any other issues remaining which the Examiner believes could be resolved through a Supplemental Response or an Examiner's Amendment, the Examiner is respectfully requested to contact the undersigned at the telephone number indicated below.

Dated: July 13, 2006

Respectfully submitted,

By 

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